

Atypical Prolymphocytic Variant of Hairy-Cell Leukemia: Case Report and Review of the Literature

Cherie H. Dunphy and Paul J. Petruska

Section of Hematopathology, Department of Pathology (C.H.D.), Section of Hematology-Oncology, Department of Internal Medicine (P.J.P.), St. Louis University Health Sciences Center, St. Louis, Missouri

The prolymphocytic variant of hairy-cell leukemia (HCL-V) is relatively rare and differs from typical hairy-cell leukemia (HCL) both clinically and morphologically. Recognition of HCL-V is important due to therapeutic impact. We report on a case of HCL-V, atypical in its degree of marrow fibrosis, IgM/lambda monoclonality, expression of CD24, and the ultrastructural presence of ribosomal lamellar complexes. The patient was treated with splenectomy followed by pentostatin, and he achieved a partial response.

© 1996 Wiley-Liss, Inc.

Key words: HCL-V, flow cytometry, ribosomal lamellar complexes

INTRODUCTION

The prolymphocytic variant of hairy-cell leukemia (HCL-V) has been described, both clinically and morphologically, as an intermediate disease between typical hairy-cell leukemia (HCL) and B-prolymphocytic leukemia (B-PLL). Patients commonly present with a high white blood cell count (WBCC) without neutropenia or monocytopenia, and have easily-aspirated bone marrows with preserved normal hemopoiesis. The cells are characterized by their intermediate size with "hairy" morphology and contain a centrally-placed nucleus with condensed nuclear chromatin and a conspicuous nucleolus. Their immunophenotype is similar to HCL (CD20+, CD19+, HLA-DR+, CD11c+, CD24-, CD10-, CD5-); however, CD25 is not expressed by HCL-V, and there is a predominance of lambda light-chain restriction, with IgG being the only heavy-chain restriction reported. Ultrastructurally, cytoplasmic pale or moderately electron-dense granules have been observed; ribosomal lamellar complexes (RLC), typically seen in HCL, have not been detected in any of 7 cases of HCL-V (Table I) [1–8]. The recognition of HCL-V has therapeutic impact, since these cases are more resistant to α -interferon or pentostatin (2'-deoxycoformycin) therapy, and show less response to splenectomy [3].

We report on the first case in the literature of HCL-V defined clinically, morphologically, and immunophenotypically by flow cytometry and immunohistochemistry, with well-defined RLC by electron microscopy (EM).

The patient underwent splenectomy, was treated with pentostatin, and at 15 months after initial presentation, was asymptomatic and hematologically stable with persistent disease. However, within the following 4 months, the patient's course became more aggressive and hospice care was necessary.

CASE REPORT

A 42-year old male presented with increasing abdominal girth and a 30-pound weight loss. Physical examination revealed marked splenomegaly without peripheral lymphadenopathy. WBCC was 58,200/ul (17% lymphocytes, 59% "atypical lymphocytes," 17% segmented neutrophils, 2% band forms, and 5% monocytes); hemoglobin (Hgb) was 6.2 g/dl; and platelet count was 141,000/ul. Computerized axial tomographic (CT) scan of the abdomen revealed splenomegaly (15.0 × 13.0 × 20.0 cm). Peripheral blood was submitted for flow cytometric analysis, and subsequently a bone-marrow biopsy was performed, with a diagnosis of the prolymphocytic variant of hairy-cell leukemia. Splenectomy was then performed due to the painful, massive splenomegaly associated with

Received for publication November 27, 1995; accepted March 6, 1996.

Address reprint requests to Dr. Cherie Dunphy, Department of Pathology, St. Louis University School of Medicine, 1402 S. Grand, St. Louis, MO 63104.

TABLE 1. Immunophenotype and EM Findings in HCL-V [1-8]*

| Pathologic findings study | Positive cases/cases examined | Present case |
|---------------------------|-------------------------------|--------------|
| CD20 | 13/14 | + |
| CD11c | 19/19 | + |
| CD5 | 0/23 | - |
| CD25 | 0/26 | - |
| sIg | 18/20 | + |
| TRAP | 9/17 | + |
| EM (RLC) | 0/7 | + |

*EM, electron microscopy; HCL-V, prolymphocytic variant of hairy-cell leukemia; TRAP, tartrate-resistant acid phosphatase; RLC, ribosomal lamellar complexes; sIg, surface immunoglobulin.

anemia. The patient was then treated with pentostatin (4 mg/m² every 2 weeks for 10 courses). Cladribine was considered but not administered due to the route of administration required in this patient with psychosocial problems.

At completion of therapy, WBCC was 18,500 (41% band forms, 3% myelocytes, 10% eosinophils, and 43% lymphocytes); Hgb was 14.0 g/dl; and platelet count was 343,000/ul. Fifteen months after initial presentation, the patient was asymptomatic. WBCC was 32,600/ul (46% segmented neutrophils, 2% band forms, 3% eosinophils, 7% monocytes, and 42% lymphocytes); Hgb was 15.8 g/dl; and platelet count was 281,000/ul. However, within 4 months, WBCC increased to 153,300/ul with 84% "lymphoid" cells. The patient was sent for hospice care.

MORPHOLOGIC ANALYSIS AND RESULTS

Light Microscopy

The Wright's-stained peripheral blood smear revealed numerous intermediate-sized cells with centrally-placed nuclei containing a single prominent nucleolus. The chromatin was condensed. There was moderate-to-abundant associated cytoplasm with irregular edges and occasional "hairy" projections. The Wright's-stained bone-marrow aspirate smears revealed similar findings. The bone-marrow core biopsy was markedly hypercellular (95% cellular), with sheets of intermediate-sized lymphoid cells with prominent nucleoli and associated diffuse, marked reticulin fibrosis (Fig. 1).

The spleen weighed 3,800 g and measured 35.0 × 19.5 cm in largest diameter. On cut surface, it was dark red and slightly firm without focal lesions. Multiple parenchymal blood lakes were noted. Wright's-stained touch preparation of spleen revealed sheets of intermediate-sized cells with central nuclei, clumped chromatin, prominent nucleoli, and moderate-to-abundant cytoplasm. Sections of B-5-fixed splenic tissue revealed marked expansion of the red pulp, which was infiltrated by sheets of cells with similar morphology to that described above. Occasional red blood cell lakes were present.

Immunohistochemistry

Acid phosphatase with and without tartrate (Sigma, St. Louis, MO) was applied to the peripheral blood smear. The peripheral blood lymphoid cells showed strong, diffuse acid phosphatase staining which was resistant to treatment with tartrate.

Flow Cytometry

Peripheral blood specimens, a bone-marrow aspirate, and an RPMI 1640 (Cellgro Mediatech Tissue Culture, Fischer Scientific, Pittsburgh, PA) suspension of spleen were analyzed on an Ortho Cytofluor absolute flow cytometer (Ortho Diagnostic Systems, Raritan, NJ) for various antigens, using standard techniques and the following commercially-available monoclonal antibodies: CD1, CD15, and HLA-DR (Ortho Diagnostic Systems); CD2, CD10, CD11c, CD13, CD14 (My4), CD19, CD20, CD33, and CD56 (Coulter Clone, Coulter Immunology, Hialeah, FL); CD3, CD4, CD7, and CD45 (Becton-Dickinson, San Jose, CA); CD5 and CD8 (Gen Trak, Inc., Wayne, PA); CD24 (Hybritech, Inc., San Diego, CA); CD25 (DAKO, Carpinteria, CA); CD34 (Gen Trak, Plymouth Meeting, PA); and IgA, IgD, IgG, IgM, kappa, and lambda (Kallesstad, Inc., Chaska, MN).

Flow cytometric analysis of the peripheral blood revealed a WBCC of 60,100/ul with 93% of cells within a combined small-intermediate cell region. Within this combined region, 90% of cells expressed CD19, CD20, CD24, CD11c, HLA-DR, and monoclonal surface IgM/lambda. CD10, CD5, and CD25 were not expressed by the monoclonal B cells. Thus, the monoclonal B cells represented 84% of the peripheral WBCC (50,484/ul).

Flow cytometric analysis of the bone-marrow aspirate revealed a WBCC of 48,600/ul, with 81% of cells within a combined small-intermediate cell region. This region was composed of 85% of cells with the same immunophenotype (CD19+, CD20+, CD11c+, HLA-DR+, and monoclonal IgM/lambda), representing 69% of the bone marrow. CD5, CD10, and CD25 were not expressed by the monoclonal B cells.

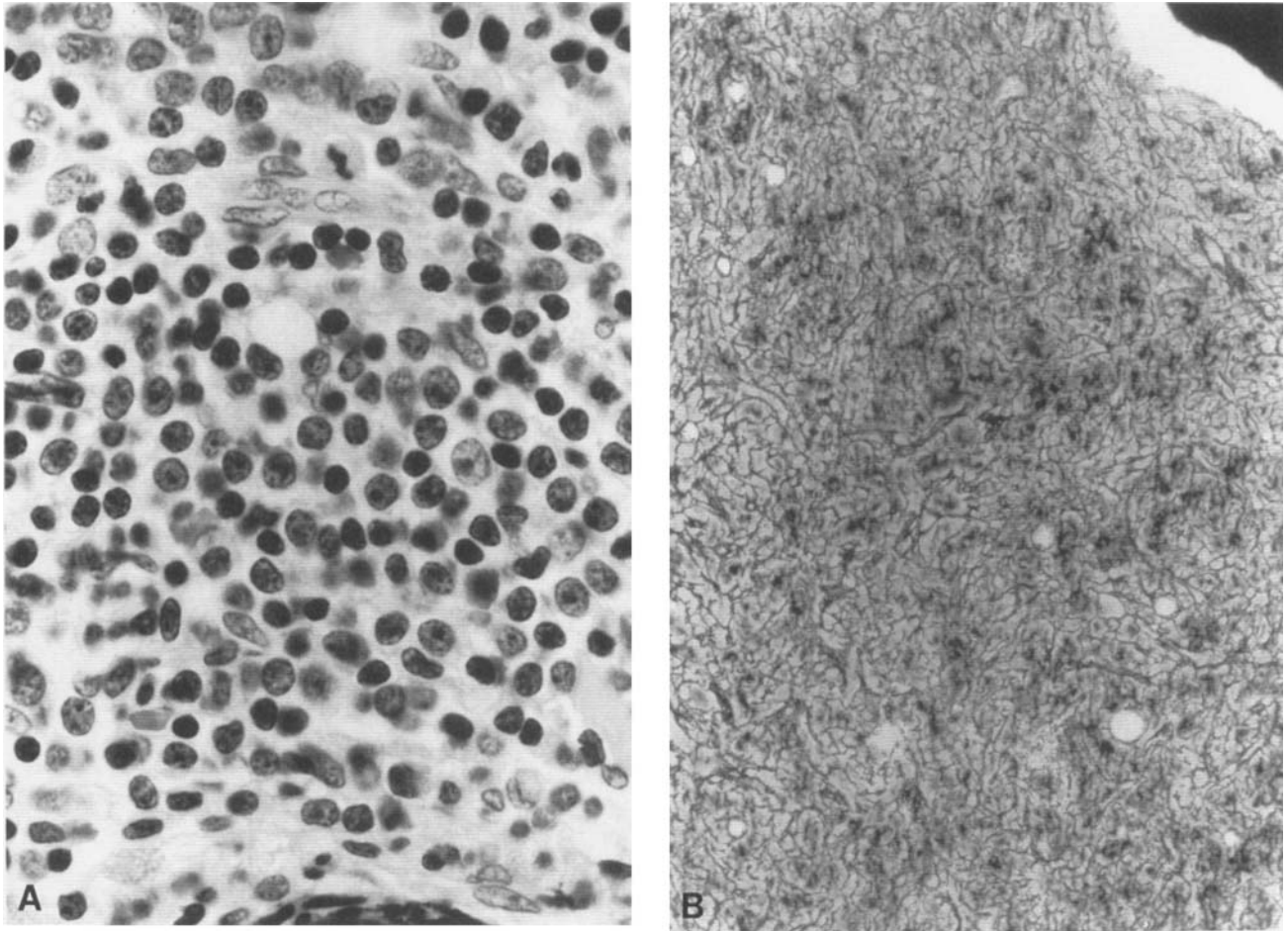


Fig. 1. Bone-marrow core biopsy of HCL-V, demonstrating (A) sheets of intermediate-sized lymphocytes with prominent nucleoli (hematoxylin and eosin, $\times 1,000$) and (B) marked reticulin fibrosis ($\times 400$).

Flow cytometric analysis of the splenic suspension revealed 94% of cells within a combined small-intermediate cell region, and 84% of these were represented by the monoclonal B cells expressing CD19, CD20, CD11c, HLA-DR, and IgM/lambda.

Flow cytometric analysis of the peripheral blood, at completion of therapy, revealed a WBCC of 18,500/ul, with 54% of cells within a combined small-intermediate cell region. This region was composed of 76% of cells with the same previous immunophenotype (CD19+, CD20+, CD24+, CD11c+, HLA-DR+, and monoclonal IgM/lambda), representing 41% of the peripheral blood WBCC (7,585/ul).

Electron Microscopy

Electron microscopic (EM) examination of the buffy-coat preparation of the peripheral blood specimen revealed numerous cells with villous projections on the

cytoplasmic surface and RLC within the cytoplasm (Fig. 2A,B).

DISCUSSION

The polymorphocytic variant of HCL is relatively rare, with only 28 cases reported in the literature [1–8]. It differs clinically from HCL in that patients generally present with a high WBCC without neutropenia or monocytopenia. The bone marrow aspirates easily, since reticulin fibrosis in the marrow is either absent or, at most, sparse-to-moderate.

The immunophenotypes of HCL and HCL-V are very similar. However, cells of HCL typically strongly express CD25, which corresponds to the α chain (p55) of IL2R, whereas cells of HCL-V lack this determinant and do not express CD25. Cells of HCL and HCL-V have a surface determinant corresponding to the β chain (p75) of IL2R

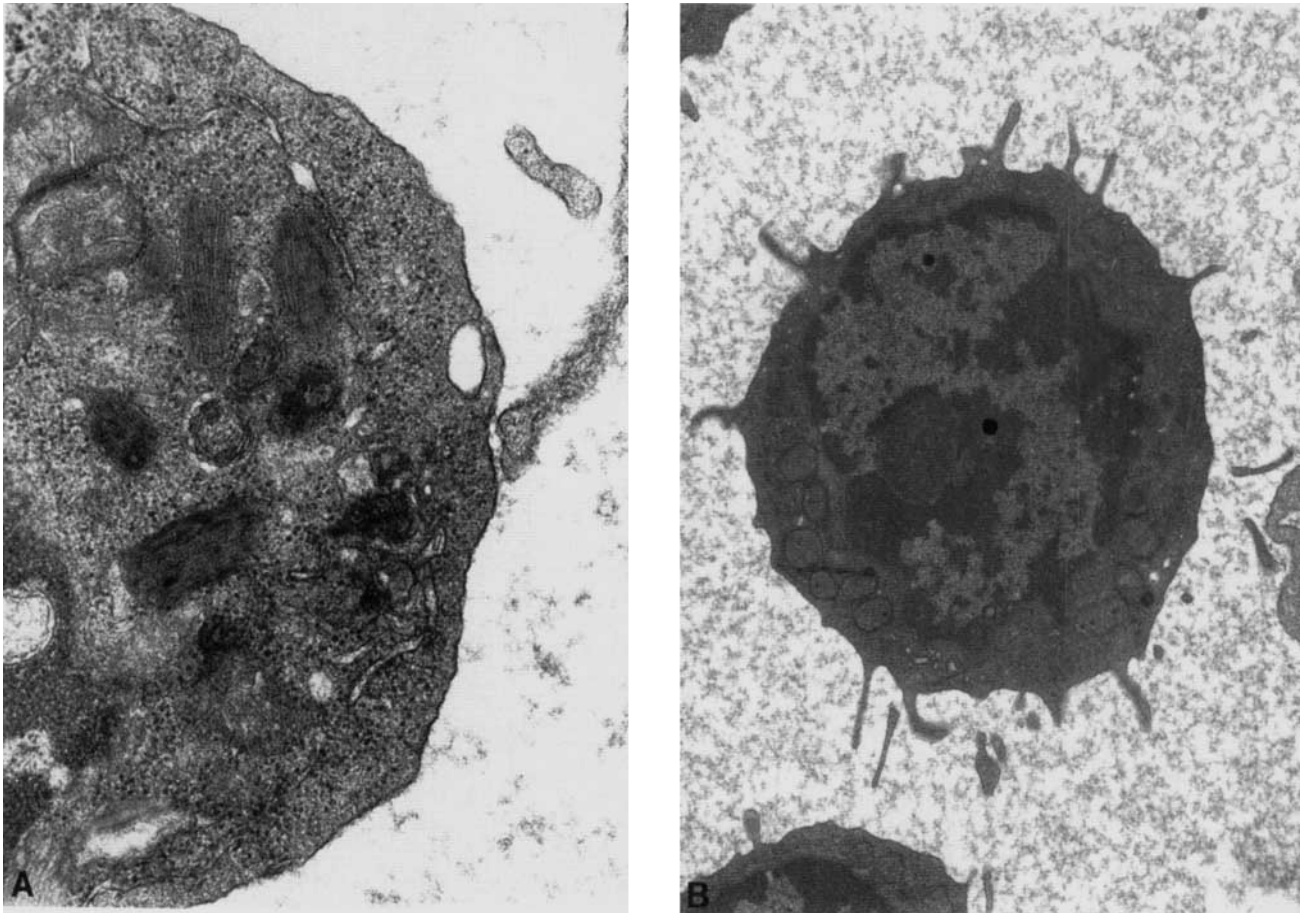


Fig. 2. Electron photomicrographs of HCL-V cells. **A:** Demonstration of cytoplasmic villous projections ($\times 5,500$). **B:** Ribosomal lamellar complexes (RLC), in longitudinal sections ($\times 507,000$).

which is not detected by CD25 [4,9,10]. The tartrate-resistant acid-phosphatase (TRAP) stain is strongly positive in as many as 99% of HCL patients, if multiple blood films or buffy-coat preparations are scanned at low power [11]. In contrast, only 60% (9/17) of HCL-V cases are TRAP-positive, and often of weak intensity. Another differential diagnostic consideration in these cases is splenic lymphoma with circulating villous lymphocytes (SLVL); however, the immunophenotype of these cells is that of a mature B cell without CD5, CD11c, or CD25 expression or tartrate-resistant acid phosphatase [12]. It is important to recognize HCL-V, since clinically these patients have not responded as well to α -interferon therapy, pentostatin therapy, or splenectomy.

This case represents an atypical HCL-V in regard to the marked bone-marrow fibrosis, the IgM/lambda monoclonality, and the presence of RLC by EM. In addition, our case had expression of CD24, which is usually absent in HCL and has never been reported in HCL-V [7,13].

Perhaps the cell of origin in our case is an earlier B cell; however, the clinical course was that of HCL-V. Nearly all patients with HCL will respond to pentostatin, and 75% of HCL patients will achieve complete remission with pentostatin [14–16]. Our patient had residual, although stable, disease at 15 months follow-up, and then had clinically progressive disease at 19 months from initial presentation. This course most likely represents a nonresponse, since pentostatin was administered immediately postsplenectomy. Of the HCL-V patients described by Sainati et al. [3], 3 were treated with pentostatin and 2 of these had a partial response as in our patient. The other had no response. It is unclear whether these 2 patients, who partially responded, had undergone a previous splenectomy; perhaps this procedure may improve the response to pentostatin in HCL-V patients, although there is no clear-cut evidence at this time.

We recommend comprehensive flow cytometric analysis with ancillary studies, including immunocytochemis-

try and electron microscopy, of these unusual "lymphoid" leukemias in order to recognize their existence, better define their natural history, and develop effective therapy.

ACKNOWLEDGMENTS

The authors thank Rosemary Baxter and Patty Jenkins for secretarial assistance, and Jesse Urhahn for photographic assistance.

REFERENCES

1. Catovsky D, O'Brien M, Melo JV, Wardle J, Brozovic M: Hairy cell leukemia (HCL) variant: An intermediate disease between HCL and B prolymphocytic leukemia. *Semin Oncol* 11:362, 1984.
2. Cawley JC, Burns GF, Hayhoe FGJ: A chronic lymphoproliferative disorder with distinctive features: A distinct variant of hairy-cell leukemia. *Leuk Res* 4:547, 1980.
3. Sainati L, Matutes E, Mulligan S, de Oliveira MP, Rani S, Lampert IA, Catovsky D: A variant form of hairy cell leukemia resistant to α -interferon: Clinical and phenotypic characteristics of 17 patients. *Blood* 76:157, 1990.
4. De Toter D, Tazzari PL, Lauria F, Raspadori D, di Celle PF, Carbone A, Gobbi M, Foa R: Phenotypic analysis of hairy cell leukemia: "Variant" cases express the interleukin-2 receptor β chain, but not the α chain (CD25). *Blood* 82:528, 1993.
5. Palomera L, Garcia Diez I, Martinez Garcia R: Variant hairy cell leukemia: Immunophenotypic and ultrastructural study. *Sangre (Bare)* 36:135, 1991.
6. Zinzani PL, Lauria F, Buzzi M, Raspadori D, Gugliotta L, Bocchia M, Macchi S, Alger R, Tura S: Hairy cell leukemia variant: A morphologic, immunologic, and clinical study of 7 cases. *Haematologica (Pavia)* 75:54, 1990.
7. Kramer PA, Oosterhuis WP, van Kammen E, Hazenberg BP, Balhuizen JC, Dinkelaar RB: A patient with a variant form of hairy cell leukemia. *Neth J Med* 43:262, 1993.
8. Machii T, Tokumine Y, Inoue R, Kitani T: Predominance of a distinct subtype of hairy cell leukemia in Japan. *Leukemia* 7:181, 1993.
9. Korsmeyer SJ, Green WC, Cossman J, Hsu S, Jensen JP, Neckers LM, Marshall SL, Bakshi A, Depper J, Leonard WJ, Jaffe ES, Waldmann TA: Rearrangement and expression of immunoglobulin genes and expression of Tac antigen in hairy cell leukemia. *Proc Natl Acad Sci USA* 80:4522, 1983.
10. Catovsky D, Foa R: "The Lymphoid Leukemias." London: Butterworths, 1990, p 156.
11. Yam LT, Janckila AJ, Li C-Y, Lam WKW: Chemistry of tartrate-resistant acid phosphatase: 15 years' experience. *Leukemia* 1:285, 1987.
12. Rousset M-C, Gardembas-Pain M, Renier G, Chevaillier A, Ifrah N: Splenic lymphoma with circulating villous lymphocytes. Report of a case with immunologic and ultrastructural studies. *Am J Clin Pathol* 97:147, 1992.
13. Jansen J, Schuit HRE, Meijer CJLM, van Nieuwkoop JA, Hijmans W: Cell markers in hairy cell leukemia studied in cells from 51 patients. *Blood* 59:52, 1982.
14. Kraut EH, Bouroncle BA, Grever MR: Pentostatin in the treatment of advanced hairy cell leukemia. *J Clin Oncol* 7:168, 1989.
15. Spiers ASD, Moore D, Cassileth PA, Harrington DP, Cummings FJ, Neiman RS, Bennett JM, O'Connell MJ: Remissions in hairy-cell leukemia with pentostatin (2'-deoxycoformycin). *N Engl J Med* 316:825, 1987.
16. Johnston JB, Eisenhauer E, Corbett WEN, Scott JG, Zaentz SD: Efficacy of 2'-deoxycoformycin in hairy cell leukemia: A study of the National Cancer Institute of Canada Clinical Trials Group. *JNCI* 80:765, 1988.